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(54) **Tape plaster comprising anthranilic acid derivatives as percutaneous absorption promotors**

Pflaster enthaltend Anthranilsäure-Derivate zur Förderung der perkutanen Absorption

Pansement contenant des derivés de l'acide anthranilique comme stimulateurs d'absorption percutanée

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- **PATENT ABSTRACTS OF JAPAN vol. 009, no. 324 (C-320), 19 December 1985 & JP 06 155111 A (HISAMITSU SEIYAKU KK)**

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Description

[0001] The present invention relates to a novel percutaneous absorption promoter. More particularly, the present invention relates to a percutaneous absorption promoter having excellent ability of promoting percutaneous absorption of a pharmacologically active substance and excellent safety simultaneously, capable of delivering the desired pharmacologically active substance rapidly to the location of treatment or to all parts of the body through the circulating system and effective for curing various lands of disease. The present invention relates also to a novel tape plaster comprising it and a novel method of promoting percutaneous absorption by utilizing it.

Prior art

[0002] During the recent progress of medical treatment, transdermal therapeutic system (TTS) have been developed to absorb percutaneously and deliver desired pharmacologically active substances to all parts of the body and thus to maintain the curing effect for a prolonged time. For example, transdermal therapeutic systems utilizing nitroglycerol or isosorbide dinitrate for curing angina pectoris, those containing clonidine for curing hypertonia and those containing estradiol for curing climacteric difficulties have actually been utilized.

[0003] However, even though these transdermal therapeutic systems show many advantages such as evasion of metabolism of the pharmacologically active substances at intestine and liver, reduction of side reactions and increased retention of the pharmacological effect, they have problem that, because skin essentially has the barrier function against invasion of foreign substances, only limited kinds of pharmacologically active substances can attain the concentration of the substances in blood high enough to show the pharmacological effect and the pharmacologically active substances which can be utilized for the transdermal therapeutic systems are naturally very limited.

[0004] Various methods have been tried to improve the percutaneous absorption of pharmacologically active substances. For example, pharmacologically active substances were modified to form prodrugs and complexes. Ionic pharmacologically active substances were utilized with use of iontophoresis. These methods have a problem that the actual administration requires detailed studies on the individual pharmacologically active substance and a long period of time and a large amount of investment are inevitably required. On the other hand, percutaneous absorption promoters which increase percutaneous absorption of pharmacologically active substances by decreasing the barrier property of skin have been actively developed. It is expected by using these percutaneous absorption promoters that various kinds of pharmacologically active substances can be utilized without much limitations.

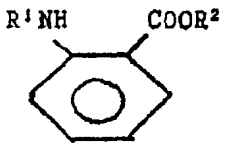
[0005] As the percutaneous absorption promoters, following compounds, for example, have been utilized: polar solvents, such as dimethylsulfoxide, decylmethylsulfoxide, dimethylformamide and dimethylacetamide; cycloalkanes, such as azacycloheptan-2-one and 1-dodecylazacycloheptan-2-one; esters of carboxylic acids and alcohols, such as isopropyl myristate and isopropyl palmitate; glycols; surface active agents, such as sodium laurylsulfate and sodium dodecylsulfate; and derivatives of fatty acids, pyroglutamic acid and urea which are natural moisturing agents of skin. These absorption promoters have problems that they do not always satisfy both of the promotion of the percutaneous absorption and safety, such as safety from toxicity and irritation, and that a long time is required to exhibit the pharmacological activity because of a long lag time in the percutaneous absorption of the pharmacologically active substances.

SUMMARY OF THE INVENTION

[0006] The present invention accordingly has an object to provide a percutaneous promoter having excellent ability of promoting the percutaneous absorption of a pharmacologically active substance and excellent safety simultaneously, capable of delivering the desired pharmacologically active substance rapidly to the location of treatment or to all parts of the body through the circulating system and effective for curing various kinds of disease. Another object of the invention is to provide a tape plaster comprising it.

[0007] Extensive investigations undertaken by the present inventors with the objects described above lead to a discovery that a derivative of amino acid having the formula [1] promotes percutaneous absorption of pharmacologically active substances remarkably and has excellent safety simultaneously. The present invention has been completed on the basis of the discovery.

[0008] Thus, the percutaneous absorption promoter of the invention comprises a derivative of amino acid having the formula:



[1]

wherein

R^1 is a hydrogen atom, an acyl group having 1 to 20 carbon atoms or a hydrocarbon group having 1 to 20 carbon atoms, and

R^2 is a hydrogen atom or a hydrocarbon group having 1 to 20 carbon atoms.

[0009] The tape plaster of the invention comprises an adhesive material comprising the percutaneous absorption promoter described above and a pharmacologically active substance coated on a tape substrate, the amount of the percutaneous absorption promoter being 5 to 50 wt.% of the total amount of the percutaneous absorption promoter composition.

[0010] The invention further provides the use of a compound of formula [1] for the preparation of a medicament wherein said compound acts as a percutaneous absorption promoter.

[0011] Other and further objects, features and advantages of the invention will appear more fully from the following description.

[0012] The invention will be described in detail in the following.

[0013] The percutaneous absorption promoter of the invention comprises a derivative of an amino acid having the formula [1].

[0014] Examples of the acyl group having 1 to 20 carbon atoms as the substituent R^1 in the formula [1] are: aliphatic acyl groups, such as formyl group, acetyl group, propanoyl group, butanoyl group, pentanoyl group, octanoyl group, decanoyl group, dodecanoyl group, tetradecanoyl group, palmitoyl group, stearoyl group, oleoyl group, and acryloyl group; aromatic acyl groups, such as benzoyl group, toluoyl group, salicyloyl group, cinnamoyl group, naphthoyl group, phthaloyl group, furoyl group and anisoyl group.

[0015] Preferable examples among the acyl groups described above are saturated and unsaturated aliphatic acyl groups having 1 to 20 carbon atoms. More preferable examples among them are saturated and unsaturated linear aliphatic acyl groups having 2 to 16 carbon atoms.

[0016] Examples of the hydrocarbon group having 1 to 20 carbon atoms as the substituent R^1 in the formula [1] are: alkyl groups, such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, tert-butyl group, pentyl group, hexyl group, heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group, hexadecyl group, heptadecyl group, octadecyl group, nonadecyl group and eicosyl group; alkenyl groups, such as ethynyl group, propenyl group, 1-butenyl group, isobutenyl group, 1-pentenyl group, 2-pentenyl group, 3-methyl-1-butenyl group, 1-hexenyl group, tetramethylethynyl group, 1-heptenyl group, 1-octenyl group, 1-nonenyl group, 1-decenyl group, 1-undecenyl group, tridecenyl group, pentadecenyl group, octadecenyl group and eicosenyl group; phenyl groups having one or more alkyl groups or alkenyl groups described above as the substituent; phenylalkyl groups having phenyl group, an alkylphenyl group or an alkenylphenyl group as the substituent to the alkyl group described above, such as benzyl group, phenylethyl group, phenylpropyl group, phenylbutyl group, phenylpentyl group and phenylhexyl group; phenylalkenyl groups having phenyl group, an alkylphenyl group or an alkenylphenyl group as the substituent to the alkenyl group described above.

[0017] Preferable examples among the hydrocarbon groups described above are saturated and unsaturated aliphatic hydrocarbons having 1 to 20 carbon atoms. More preferable examples among them are saturated and unsaturated linear aliphatic hydrocarbons having 1 to 20 carbon atoms and most preferable examples among them are saturated and unsaturated linear aliphatic hydrocarbons having 1 to 16 carbon atoms.

[0018] Examples of the hydrocarbon group having 1 to 20 carbon atoms as the substituent R^2 in the formula [1] are the same as the examples of the hydrocarbon group having 1 to 20 carbon atoms as the substituent R^1 in the formula [1]. Preferable examples among them are saturated and unsaturated aliphatic hydrocarbon groups having 1 to 20 carbon atoms and more preferable examples among them are saturated and unsaturated hydrocarbon groups having 1 to 12 carbon atoms.

[0019] The derivatives of the amino acids are preferably compounds having the formula [1] wherein R^1 is a saturated or unsaturated linear aliphatic acyl group having 2 to 16 carbon atoms and R^2 is a saturated or unsaturated linear aliphatic hydrocarbon group having 1 to 4 carbon atoms and, more preferably, compounds having the formula [1] wherein R^1 is a saturated or unsaturated linear aliphatic acyl group having 8 to 12 carbon atoms and R^2 is a saturated

or unsaturated linear aliphatic hydrocarbon group having 1 to 4 carbon atoms.

[0020] The derivatives of the amino acids may be any of L-isomers, D-isomers and racemic isomers.

[0021] Examples of the derivatives of the amino acids are: ethyl anthranilate, octyl anthranilate, stearyl anthranilate, N-butyloylanthranilic acid, ethyl N-butyloylanthranilate, octyl N-butyloylanthranilate, stearyl N-butyloylanthranilate, N-octanoylanthranilic acid, N-decanoylanthranilic acid, N-dodecanoylanthranilic acid, methyl N-dodecanoylanthranilate, ethyl N-dodecanoylanthranilate, butyl N-dodecanoylanthranilate, octyl N-dodecanoylanthranilate, stearyl N-dodecanoylanthranilate, N-myristoylanthranilic acid, methyl N-myristoylanthranilate, ethyl N-myristoylanthranilate, butyl N-myristoylanthranilate, N-palmitoylanthranilic acid, N-stearoylanthranilic acid, octyl N-stearoylanthranilate and stearyl N-stearoylanthranilate.

[0022] The derivatives of the amino acids having the formula [1] can be prepared by various conventional methods.

[0023] An acyl group having 1 to 20 carbon atoms can be introduced as the substituent R^1 of the amino group in the amino acid, for example, by the reaction of the amino acid with an acid halide having the desired number of carbon atoms. In this method, the amino group can be modified with the acyl group having 1 to 20 carbon atoms by dissolving the amino acid to be modified in an aqueous solution containing a scavenger of a hydrogen halide like sodium hydroxide, then adding an aqueous solution of a carboxylic acid halide having 1 to 20 carbon atoms and an aqueous solution containing the scavenger of the hydrogen halide to the above solution and allowing the reaction to proceed.

[0024] A hydrocarbon group having 1 to 20 carbon atoms can be introduced as the substituent R^1 of the amino group in the amino acid, for example, by the reaction of the amino acid with an alkyl ester of p-toluenesulfonic acid having the desired number of carbon atoms. A hydrocarbon group having 1 to 20 carbon atoms can be introduced as the substituent R^2 of carboxylic group in the amino acid, for example, by dropping thionyl chloride into an alcohol having the desired number of carbon atoms, then adding an animo acid or an amino acid having a subsituent R^1 described above to the solution and then allowing the reaction to proceed.

[0025] The percutaneous absorption promoter is utilized in combination with pharmacologically active substances and applied to a patient percutaneously and locally. The kind of the pharmacologically active substance is not particularly limited but suitable substances can be selected and utilized from the generally known pharmacologically active substances.

[0026] Examples of the pharmacologically active substance are: steroid anti-inflammatory drugs, such as prednisolone, dexamethasone, hydrocortisone, fluocinolone acetonide, betamethasone varelate and betamethasone dipropionate; non-steroid anti-inflammatory drugs, such as indomethacin, diclofenac, ibufenac, ibuprofen, ketoprofen, flufenamic acid, mefenamic acid, phenylbutazone and methyl salicylate; antihistamic drugs, such as diphenhydramine, chlorpheniramine, promethazine and tripelenamine; central nervous system acting drugs, such as chlorpromazine, nitrazepam, diazepam, phenobarbital and reserpine; hormones, such as insuline, testosterone, methyltestosterone, progesterone and estradiol; antihypertensive drugs, such as clonidine, reserpine and guanethidine sulfate; cardiotonics, such as digitoxin and digoxine; antiarrhythmic drugs, such as propranolol hydrochloride, procainamide hydrochloride, ajmaline and pindolol; coronary vaso dilators, such as nitroglycerin, isosorbide dinitrate, erythritose tetranitrate, papaverine hydrochloride and nifedipine; local anesthetics, such as lidocaine, benzocaine and procaine hydrochloride; hypnotics and sedatives, such as barbital, thiopental, phenobarbital and cyclobarbital; analgesics, such as morphine, aspirin, codeine, acetanilide and aminopyrine; antibiotics, such as pencillin, tetracycline, erythromycin, streptomycin and gentamicin; fungicides, such as benzalkonium chloride, acetophenylamine, nitrofurazone, pentamycin and naphthiomate; anticancer drugs, such as 5-fluorouracil, busulfan, actinomycin, bleomycin and mitomycin; diuretics, such as hydrochlorothiazide, penflutide and reserpine; parasympatholytic drugs, such as scopolamine and atropine; antiepileptics, such as nitrazepam and meprobamate; antiparkinsonism drugs, such as chlorzoxazone and levodopa; sulfa drugs, such as sulfamine, sulfamonomethoxine and sulfamethizole; vitamins; prostaglandins; antipasm drugs; and contraceptives. Acidic pharmacologically active substances are preferable and acidic pharmacologically acidic substances having a carboxylic group are more preferable.

[0027] Examples of the acidic pharmacologically active substance having carboxylic group are ibuprofen, flurbiprofen, phenoprofen, diclofenac, ibufenac, mefenamic acid, flufenamic acid, salycilic acid and acetylsalycilic acid. Examples of the acidic pharmacologically active substance having no carboxylic group are: phenylbutazone, ketophenylbutazone, oxyphenbutazone, phenobarbital, amobarbital and cyclobarbital.

[0028] The pharmacologically active substance can be used singly or as a combination of two or more kinds.

[0029] The percutaneous absorption promoter of the invention may be, according to desire, utilized in combination with various kinds of pharmacologically allowable additives, such as stabilizers, anti-aging agents, antioxidants, perfumes, fillers and other percutaneous absorption promoters.

[0030] The form of the compositions is as tape plasters.

[0031] As the base of ointments and creams, fatty oils, lanolin, vaselin, paraffines, plastibases, glycols, higher fatty acids and higher alcohols are utilized. If necessary, stabilizers, preservatives, emulsifiers and dispersants may be added to the base. As the base of lotions, ethanol, glycerol and glycols are utilized. As the base of liquids, ethanol, purified water and glycols are utilized.

[0032] Examples of the base of cataplasmas are natural polymers, such as gelatin, sodium alginate, corn starch, traganth gum and casein; celluloses, such as methyl cellulose, ethyl cellulose, hydroxyethyl cellulose and carboxymethyl cellulose; starches, such as dextran and carboxymethyl starch; and synthetic polymers, such as polyvinyl alcohol, sodium polyacrylate, polyvinyl pyrrolidone and polyvinyl ether. If necessary, moisturing agents, such as glycerol, propylene glycol, inorganic fillers, such as kaolin, bentonite, zinc oxide, and thickness adjusting agents, pH adjusting agents may be compounded to the base.

[0033] As the adhesive for tapes and patches, for example, acrylic adhesives, rubber adhesives and silicone adhesives are utilized.

[0034] The adhesives can be made into microreservoir-type materials by dispersing the pharmacologically active substance or a mixture of the pharmacologically active substance and a water soluble polymer within the adhesives. Dispersion of adhesives containing the pharmacologically active substance within the base of cataplasma can also be utilized.

[0035] The acrylic adhesives comprise, as the main component thereof, at least one polymer selected from the group consisting of homopolymers of acrylic esters, copolymers comprising two or more kinds of acrylic ester units and copolymers of acrylic esters.

[0036] Examples of the acrylic ester are butyl (meth)acrylate, pentyl (meth)acrylate, hexyl (meth)acrylate, heptyl (meth)acrylate, octyl (meth)acrylate, nonyl (meth)acrylate and decyl (meth)acrylate. Examples of the functional monomer are monomers containing a hydroxyl group, such as hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate, and monomers containing an amide group, such as (meth)acrylamide and dimethyl (meth)acrylamide.

[0037] The acrylic adhesives can be generally divided into solvent type adhesives and emulsion type adhesives. The solvent type adhesives generally comprise the acrylic polymer, solvents, crosslinking agents, adhesion promoters if desired and other ingredients. As the crosslinking system, the methylol group crosslinking system, the ionic crosslinking system, the urethane crosslinking system, the epoxy crosslinking system or the like are utilized.

[0038] The emulsion type adhesives generally comprise the acrylic polymer, emulsifiers, aqueous solvents, adhesion promoters if desired and other ingredients.

[0039] The rubber adhesives comprise, as the main components thereof, at least one polymer selected from the group consisting of natural rubber, polyisoprene rubber, polyisobutylene rubber, styrene-butadiene-styrene block copolymer and styrene-isoprene-styrene block copolymer.

[0040] Adhesion promoters, plasticizers, antioxidants, fillers and the like may be compounded with the rubber adhesives, if desired. The solvent type adhesives and the emulsion type adhesives using rubber latices are preferably utilized.

[0041] The silicone adhesives comprise, as the main components thereof, polydimethylsiloxane and polydiphenylsiloxane. The solvent type adhesives comprising adhesive promoters plastisizers and filler are preferably utilized.

[0042] The adhesion promoters compounded with the adhesives according to the desire are, for example, natural resins, such as rosin resins and polyterpene resins, petroleum resins such as C_5 resins, C_9 resins and DCPD resins and synthetic resins, such as coumarone-indene resins, and xylene resins.

[0043] The base utilized for the tape plasters are, for example, sheets and films of synthetic resins, such as polyester, polyvinyl chloride, polypropylene, polyethylene polyurethane, synthetic papers, sheets and films of cellulose, nonwoven fabrics, woven fabrics and knitted fabrics.

[0044] The amount of application of the percutaneous absorption promoter of the invention can be suitably selected according to the mode and the condition of the application. It is generally in the range from 0.1 to 50 weight %, preferably in the range from 0.5 to 30 weight % based on the total amount of the transdermal therapeutic formulation comprising the percutaneous absorption promoter. When the percutaneous absorption promoter is utilized in tape plasters, the amount is in the range from 5 to 30 weight % on the same basis.

[0045] The amount of the pharmacologically active substance is preferably in the range from 0.5 to 20 weight %, more preferably in the range from 1 to 10 weight %, based on the total amount of the transdermal therapeutic formulation.

[0046] It is the general understanding that the barrier property of skin against foreign substances has the basis on the structure of stratum corneum. This is more easily understood when one observes remarkably increased penetration of pharmacologically active substances through skin when the surface of the skin is partially removed by some cause, for example by cleavage of tape attached to the skin. The stratum corneum of skin is composed of layers of keratin cells which are made of proteins of flattened structures. It is generally understood that there are two main routes of passage for pharmacologically active substances: the transcellular route which is the passage through cells and the intercellular route which is the passage through interstices between cells. The stratum corneum cells are composed of keratin and lipids and, at the intercellular route, lamella layers are formed by amphiphillic materials such as phospholipids and the like, thus hydrophillic layers and lipophillic layer being accumulated to form a multilayer area. In the hydrophillic layers, molecules of water aggregate together to form clusters. Both of the hydrophillic and lipophillic layers show high resistance against diffusion of foreign substances and it is generally understood that the barrier property of

skin is caused by the tight structure of the skin layers as described here.

[0047] The derivatives of amino acids having the formula [1] have particularly high affinity to lipids and give fluctuations to the lipids, this condition being considered to cause decrease of the resistance against diffusion and increase of the permeation of the pharmacologically active substances. The derivatives of amino acids are considered to affect the structure of water molecule by the effect on the lipids as well, to cause increase of the permeation of the substances.

[0048] The percutaneous absorption promoter of the invention is a derivative of amino acids having the same backbone structure as that of the amino acids showing the function of vitamin L1, one of the vitamins found in the body. It is therefore decomposed to compounds harmless to the body by enzymes in the body, such as esterase, peptidase and the like.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0049] The invention will be understood more readily with reference to the following examples.

Example of preparation of derivatives of anthranilic acid

Example of preparation of material 1

Synthesis of N-n-octanoylanthranilic acid

[0050] Anthranilic acid was dissolved in a mixed solvent containing pyridine and tetrahydrofuran (THF) in 5 : 5 ratio and a THF solution of n-caprioyl chloride was dropped to the solution during several hours for reaction. After the reaction, hydrochloric acid was added to the reaction mixture. Pyridine hydrochloride was filtered and the solvent was removed. N-n-octanoylanthranilic acid was obtained from the remaining reactant after the purification by column chromatography with the yield of 79.4 %.

Example of preparation of material 2

Synthesis of N-n-octylanthranilic acid

[0051] To a solution of anthranilic acid in toluene, n-octyl p-toluenesulfonate prepared according to the conventional method was added and the mixture was refluxed at 120°C. After 6 hours, an aqueous solution of sodium hydroxide was added and the toluene layer was concentrated. N-n-octylanthranilic acid was obtained from the remaining reactant after the purification by column chromatography with the yield of 43.1 %.

Example of preparation of material 3

Synthesis of ethyl N-n-octanoylanthranilate

[0052] Thionyl chloride was dropped to ethanol and the mixture was stirred for 2 hours. Then, N-n-octanoylanthranilic acid was added to the mixture and reaction was allowed to proceed for 3 days at the room temperature. After the reaction, the solvent was removed and ethyl N-n-octanoylanthranilate was obtained from the remaining reactant after the purification by column chromatography with the yield of 89.2 %.

[0053] Various kinds of derivatives of anthranilic acid shown in Table 1 were prepared by the similar methods to the above.

[0054] The acyl groups and the carboxyl groups used for modifying the amino group in Examples of preparation of material 1 to 3 were normal isomers in all cases.

Example 1

Percutaneous permeability test

[0055] In a vertical Franz type cell, a piece of skin taken from abdomen of a Wister rat was used as the permeation membrane. As the donor solution, a solution of indomethacin as the model pharmacologically active substance and a derivative of anthranilic acid (1 weight %, respectively) in a 50 % aqueous solution of ethanol was used. As the receiver solution of the permeation, a buffer solution of phosphoric acid of pH 7.2 was used. Concentration of the pharmacologically active substance in the receiver solution was measured with time by high performance liquid chromatography (HPLC).

[0056] Ratio of the peak areas of the pharmacologically active substance and the internal standard substance was obtained from the HPLC chart. The concentration of the pharmacologically active substance was obtained by using the calibration curve which had been made beforehand. (The method of internal standard)

[0057] Table 1 shows the value of the accumulated permeation of every derivative of anthranilic acid based on the value of the control run. The value was obtained as the ratio of the concentrations of the pharmacologically active substance in the presence and in the absence of a derivative of anthranilic acid after the permeation of 24 hours.

Table 1

derivative of anthranilic acid	permeation based on the control
anthranilic acid	1.86
N-acetylanthranilic acid	1.94
N-n-octanoylanthranilic acid	2.46
N-n-dodecanoylanthranilic acid	2.28
N-n-octadecanoylanthranilic acid	2.14
ethyl N-acetylanthranilate	2.04
n-butyl N-acetylanthranilate	3.69
ethyl N-n-octanoylanthranilate	4.29
n-butyl N-n-octanoylanthranilate	3.46
lauryl N-n-octanoylanthranilate	3.16
methyl N-n-dodecanoylanthranilate	2.43
ethyl N-n-dodecanoylanthranilate	4.00
n-butyl N-n-dodecanoylanthranilate	2.63
ethyl N-n-octadecanoylanthranilate	2.41
n-butyl N-n-octadecanoylanthranilate	2.33
lauryl N-n-octadecanoylanthranilate	2.10
stearyl N-n-octadecanoylanthranilate	1.89
stearyl N-n-octanoylanthranilate	2.01
methyl anthranilate	2.36
ethyl anthranilate	2.60
n-butyl anthranilate	4.14
n-octyl anthranilate	3.97
lauryl anthranilate	3.81
stearyl anthranilate	2.10
N-n-octylanthranilic acid	2.05
ethyl N-n-octylanthranilate	2.45

Example 2

[0058] Activity of promoting the percutaneous absorption of ethyl N-n-octanoylanthranilate prepared in Example of preparation of material 3 was evaluated by using indomethacin, sodium salicylate or ketoprofen, predonisolone and pindolol as the pharmacologically active substance according to the same method as in Example 1. Results of the evaluation are shown in Table 2. The values shown were measured after 24 hours and expressed as the value based on the control.

Table.2

pharmacologically active substance	result based on control
indomethacin	4.29
sodium salicylate	1.37
ketoprofen	3.25
predonisolone	5.86
pindolol	9.88

Example 3

Preparation of tape plaster comprising derivatives of anthranilic acid

[0059] n-Butyl acrylate was dissolved in ethyl acetate to form a 40 weight % solution and 0.4 mol % of azo-isobutyronitrile was added to the solution as the initiator. The reaction mixture was allowed to polymerize under nitrogen stream at 70°C for 8 hours. Into the polymer solution thus prepared, 20 weight parts of indomethacin and 20 weight parts of ethyl N-n-octanoylanthranilate based on 100 weight parts of the solid polymer were dissolved. The solution was cast on a polyester film and dried at 100°C for 1 minute to form an adhesive layer of 30 μm. A polyester film which had been treated with release coating was attached to the adhesive layer to prepare the tape plaster.

Percutaneous permeability test

[0060] In a vertical Franz type cell, a piece of skin taken from abdomen of a hairless rat was used as the permeation membrane. The tape plaster prepared above was applied to the skin. As the receiver solution of permeation, a buffer solution of phosphoric acid of pH 7.2 was used. Concentration of the pharmacologically active substance in the receiver solution was measured with time by high performance liquid chromatography (HPLC). Results are shown in Table 3.

Table 3

	permeation of the active substance μg/ cm^2·24hr	value based on the control
Comparative example as the control	85	-
Example containing the promoter	330	3.88

In Table 3, ethyl N-n-octanoylanthranilate was not used in Comparative example while it was used in Example.

Irritation test to skin

[0061] Irritation test to skin was made on 10 male persons of the age of 25 to 30. A tape plaster containing the derivative of anthranilic acid prepared above was applied to the inside of an upper arm and condition of the skin was examined by visual observation. Results are shown in Table 4. The results are expressed in terms of the following notations.

++: remarkable erythema or edema
+: erythema or edema
-: no change

Table 4

test number (person)	tape plaster containing the promoter	control
1	-	-
2	-	+
3	-	-
4	-	-
5	-	-

Table 4 (continued)

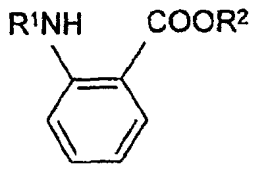
test number (person)	tape plaster containing the promoter	control
6	-	-
7	+	+
8	-	-
9	-	-
10	+	-

[0062] To summarize the advantages obtained by the invention, the percutaneous promoter of the invention has excellent ability of promoting the percutaneous absorption of the pharmacologically active substances and excellent safety simultaneously, capable of delivering the desired pharmacologically active substances rapidly to the location of treatment or to all parts of the body through the circulating system and effective for curing various kinds of disease. The tape plaster comprising it and the method of promoting percutaneous absorption by utilizing it have the same advantages.

Claims

1. A tape plaster containing a percutaneous absorption promotor composition which comprises

   (a) a pharmacologically active substance; and
   (b) a derivative of an amino acid having the formula:



   wherein

   R^1 is a hydrogen atom, an acyl group having 1 to 20 carbon atoms or a hydrocarbon group having 1 to 20 carbon atoms, and
   R^2 is a hydrogen atom or a hydrocarbon group having 1 to 20 carbon atoms,

   the amount of the derivative of the amino acid being 5 to 50 wt.% of the total amount of the percutaneous absorption promotor composition.

2. The tape plaster of claim 1, wherein R^1 is a saturated or unsaturated aliphatic acyl group having 1 to 20 carbon atoms or a saturated or unsaturated hydrocarbon group having 1 to 20 carbon atoms and R^2 Is a saturated or unsaturated aliphatic hydrocarbon group having 1 to 20 carbon atoms.

3. The tape plaster of claim 1 or 2, wherein R^1 is a saturated or unsaturated linear aliphatic acyl group having 2 to 16 carbon atoms or a saturated or unsaturated aliphatic hydrocarbon group having 1 to 20 carbon atoms and R^2 is a saturated or unsaturated aliphatic hydrocarbon group having 1 to 20 carbon atoms.

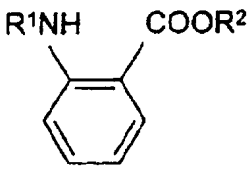
4. The tape plaster of any of claims 1 to 3 , wherein R^1 is a saturated or unsaturated linear aliphatic acyl group having 2 to 16 carbon atoms or a saturated or unsaturated aliphatic hydrocarbon group having 1 to 16 carbon atoms and R^2 is a saturated or unsaturated aliphatic hydrocarbon group having 1 to 12 carbon atoms.

5. The tape plaster of any of claims 1 to 4, wherein the pharmaceutical active substance is selected from the group consisting of indomethacin, ketoprofen, predonisolon and pindolol.

6. The tape plaster of any of the previous claims which comprises an adhesive material and a percutaneous absorption

promoter composition of any of claims 1 to 5 coated on a tape substrate.

7. The use of a derivative of an amino acid having the formula



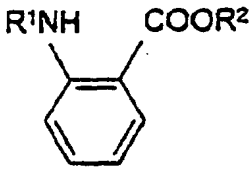
wherein R^1 is a hydrogen atom, an acyl group having 1 to 20 carbon atoms or a hydrocarbon group having 1 to 20 carbon atoms, and
R^2 is a hydrogen atom or a hydrocarbon group having 1 to 20 carbon atoms

for the preparation of a medicament wherein said derivative of an amino acid acts as a percutaneous absorption promotor.

Patentansprüche

1. Pflaster, welches eine Zusammensetzung mit einem perkutanen Absorptionspromoter enthält, die

(a) eine pharmakologisch aktive Substanz, und
(b) ein Derivat einer Aminosäure mit der Formel



umfasst, worin R^1 ein Wasserstoffatom, eine Acylgruppe mit 1 bis 20 Kohlenstoffatomen oder eine Kohlenwasserstoffgruppe mit 1 bis 20 Kohlenstoffatomen ist, und R^2 ein Wasserstoffatom oder eine Kohlenwasserstoffgruppe mit 1 bis 20 Kohlenstoffatomen ist, wobei die Menge des Derivats der Aminosäure 5 bis 50 Gewichtsprozent der Gesamtmenge der Zusammensetzung mit dem perkutanen Absorptionspromoter ist.

2. Pflaster nach Anspruch 1, worin R^1 eine gesättigte und ungesättigte, aliphatische Acylgruppe mit 1 bis 20 Kohlenstoffatomen oder eine gesättigte oder ungesättigte Kohlenwasserstoffgruppe mit 1 bis 20 Kohlenstoffatomen ist, und R^2 eine gesättigte oder ungesättigte, aliphatische Kohlenwasserstoffgruppe mit 1 bis 20 Kohlenstoffatomen ist.

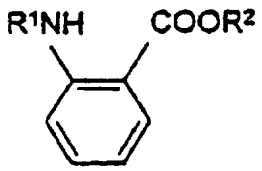
3. Pflaster nach Anspruch 1 oder 2, worin R^1 eine gesättigte oder ungesättigte, lineare, aliphatische Acylgruppe mit 2 bis 16 Kohlenstoffatomen oder eine gesättigte oder ungesättigte, aliphatische Kohlenwasserstoffgruppe mit 1 bis 20 Kohlenstoffatomen ist, und R^2 eine gesättigte oder ungesättigte, aliphatische Kohlenwasserstoffgruppe mit 1 bis 20 Kohlenstoffatomen ist.

4. Pflaster nach einem der Ansprüche 1 bis 3, worin R^1 eine gesättigte oder ungesättigte, lineare, aliphatische Acylgruppe mit 2 bis 16 Kohlenstoffatomen oder eine gesättigte oder ungesättigte, aliphatische Kohlenwasserstoffgruppe mit 1 bis 16 Kohlenstoffatomen ist, und R^2 eine gesättigte oder ungesättigte, aliphatische Kohlenwasserstoffgruppe mit 1 bis 12 Kohlenstoffatomen ist.

5. Pflaster nach einem der Ansprüche 1 bis 4, worin die pharmazeutisch aktive Substanz aus der Gruppe ausgewählt ist, die aus Indomethacin, Ketoprofen, Predonisolon und Pindolol besteht.

6. Pflaster nach einem der vorangehenden Ansprüche, welches ein Klebstoffmaterial und eine Zusammensetzung mit einem perkutanen Absorptionspromoter nach einem der Ansprüche 1 bis 5 umfasst, die auf einem Pflastersubstrat angeordnet sind.

7. Verwendung eines Derivats einer Aminosäure mit der Formel

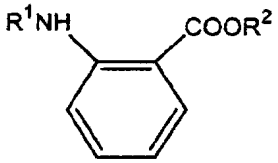


worin R^1 ein Wasserstoffatom, eine Acylgruppe mit 1 bis 20 Kohlenstoffatomen oder eine Kohlenwasserstoffgruppe mit 1 bis 20 Kohlenstoffatomen ist, und R^2 ein Wasserstoffatom oder eine Kohlenwasserstoffgruppe mit 1 bis 20 Kohlenstoffatomen ist, für die Herstellung eines Medikamentes, worin das Derivat einer Aminosäure als ein perkutaner Absorptionspromoter wirkt.

Revendications

1. Emplâtre pour bande contenant une composition d'activateur d'absorption percutanée qui comprend :

(a) une substance pharmacologiquement active ; et
(b) un dérivé d'acide aminé ayant pour formule :



dans laquelle

R^1 est un atome d'hydrogène, un groupe acyle ayant 1 à 20 atomes de carbone ou un groupe hydrocarboné ayant 1 à 20 atomes de carbone, et
R^2 est un atome d'hydrogène ou un groupe hydrocarboné ayant 1 à 20 atomes de carbone,

la quantité du dérivé de l'acide aminé étant de 5 à 50% en poids de la quantité totale de la composition d'activateur d'absorption percutanée.

2. Emplâtre pour bande de la revendication 1, dans lequel R^1 est un groupe acyle aliphatique saturé ou insaturé ayant 1 à 20 atomes de carbone ou un groupe hydrocarboné saturé ou insaturé ayant 1 à 20 atomes de carbone et R^2 est un groupe hydrocarboné aliphatique saturé ou insaturé ayant 1 à 20 atomes de carbone.

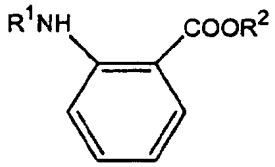
3. Emplâtre pour bande de la revendication 1 ou 2, dans lequel R^1 est un groupe acyle aliphatique linéaire saturé ou insaturé ayant 2 à 16 atomes de carbone ou un groupe hydrocarboné aliphatique saturé ou insaturé ayant 1 à 20 atomes de carbone et R^2 est un groupe hydrocarboné aliphatique saturé ou insaturé ayant 1 à 20 atomes de carbone.

4. Emplâtre pour bande de l'une quelconque des revendications 1 à 3, dans lequel R^1 est un groupe acyle aliphatique linéaire saturé ou insaturé ayant 2 à 16 atomes de carbone ou un groupe hydrocarboné aliphatique saturé ou insaturé ayant 1 à 16 atomes de carbone et R^2 est un groupe hydrocarboné aliphatique saturé ou insaturé ayant 1 à 12 atomes de carbone.

5. Emplâtre pour bande de l'une quelconque des revendications 1 à 4, dans lequel la substance active pharmaceutique est choisie dans le groupe constitué de l'indométacine, du kétoprofène, de la prednisolone et du pindolol.

6. Emplâtre pour bande de l'une quelconque des revendications précédentes qui comprend un matériau adhésif et une composition d'activateur d'absorption percutanée de l'une quelconque des revendications 1 à 5 appliquée sur un substrat de bande.

7. Utilisation d'un dérivé d'acide aminé ayant pour formule



dans laquelle R^1 est un atome d'hydrogène, un groupe acyle ayant 1 à 20 atomes de carbone ou un groupe hydrocarboné ayant 1 à 20 atomes de carbone, et
R^2 est un atome d'hydrogène ou un groupe hydrocarboné ayant 1 à 20 atomes de carbone

pour la préparation d'un médicament où ledit dérivé d'acide aminé joue le rôle d'activateur d'absorption percutanée.